

REMARKS

In the outstanding Office action, claims 1 to 20 were presented for examination. Claims 1-7 and 9-20 were rejected. Claim 8 was withdrawn from prosecution.

In this amendment applicant has amended claims 1-4, 7, 9-11 and 19-20 and has added new claims 21-23? more particularly pointing out the invention. Claim 8 has been cancelled. Accordingly, as will be discussed in detail below, it is believed that the application is in condition for allowance. Favorable reconsideration is respectfully requested.

Specification

The specification has been amended to add a cross-reference paragraph pursuant to the request in the Office action.

Claim Amendments

Claim 1 has been amended, without narrowing, to make explicit matter that was inherent in the claim before amendment by reciting that each of Xaa and Yaa is an amino acid. Support for this amendment can be found at page 3, lines 21-22 and elsewhere in applicant's specification. Other minor clerical amendments have been made to claim 1, without narrowing.

In addition, Claim 1 has been amended, without narrowing, to make explicit matter that was inherent in the claim before amendment, by specifying that the recited glass transition temperature is calculated according to a formula of Matveev et al. Support for this amendment can be found at page 3, lines 7-8 and page 6, lines 6-8 of applicant's specification.

Claims 2-4, 7, 10-11 and 19-20 have been amended to delete the preferred alternatives that apparently provided a basis for rejection.

Claim 9 has been amended in a similar manner to claim 1 and the support for the amendments is similar.

New claims 21-23 have been added to claim the alternative subject matters deleted from claims 4, 10 and 11.

Claim Rejections - 35 U.S.C. § 112 Second Paragraph

Claims 1-7 and 9-20 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Claims 1-7 and 9-20, as now amended, are respectfully believed free of any basis for rejection on this ground and accordingly are believed to be definite.

With regard to the definition of the Gly-Xaa-Yaa triplets, it is believed that a person of ordinary skill in the art will understand that either of the terms "Xaa" or "Yaa" can be any amino acid, as may be seen, for example, from EP 0926543 and 1014176 cited at page 11, line 31 of applicant's specification. In addition, the sequences and the sequence listing in applicant's specification provide a large number of examples of possible amino acid embodiments of Xaa and Yaa, for example in the portion of SEQ ID NO: 1 appearing at page 7, line 16 to page 8, line 5.

Claims 2-4, 7, 10-11 and 19-20, as now amended, are believed definite, in light of the deletion of the preferred alternatives that apparently provided a basis for rejection.

Claim Rejections - 35 U.S.C. § 102(b) Alleged Anticipation

Claims 1-7 and 9-20 were anticipated under 35 U.S.C. § 102(b) by Chang et al. WO 01/34801 ("Chang et al. '801" herein) or by Chang et al WO 01/34646 ("Chang et al. '646 herein).

Specifically, it is admitted in the Office action that neither reference explicitly teaches a glass transition temperature of greater than 180° C. However it is argued in

the Office action that "this property is believed to be inherently present in the recombinant gelatin of Chang et al. because Chang et al. teach a recombinant gelatin-like polypeptide that allegedly meets the chemical and/or structural limitations of the instant recombinant gelatin-like polypeptide, the argument being made in similar terms for each reference.

This argument is respectfully believed to be defective because it fails to take account of an important claim limitation, namely that the recombinant gelatin-like polypeptide recited in applicant's claims 1 and 9 must also have, in addition to its chemical and structural limitations, a calculated glass transition temperature of higher than 180 degrees Celsius. This property can equally well distinguish the recombinant gelatin-like polypeptide, and thus the lyophilized composition, from each of the cited references, just as much as a chemical or structural limitation can. Thus, gelatin-like polypeptides having a calculated glass transition temperature which is lower than 180 degrees Celsius, which includes the disclosures of both Chang et al. references, are excluded from the scope of claim 1 or of claim 9. Accordingly, each of claims 1 and 9 is believed patentably distinguished from either Chang et al. reference for this reason alone.

Furthermore, applicant does not believe that any of the recombinant gelatin-like polypeptides disclosed in either of the Chang et al. references inherently has a calculated glass transition temperature ("Tg" herein) of higher than 180 degrees Celsius, for the entire polypeptide, as will now be explained.

As described in applicant's specification, the claimed Tg is not an intrinsic property of known gelatin-like polypeptides, but is a property which can be provided by following the directions in applicant's specification, or by other methods that will be, or become, apparent to a person of ordinary skill in the art, in light of applicant's disclosure.

The invention claimed in claims 1 and 9 relates to the use of particular gelatin-like polypeptides as improved stabilizers of lyophilized substances. The description at page 4, lines 20-24 of applicant's specification explains that when one scans a native gelatin amino acid sequence using a Tg moving average it was found that the Tg was not uniformly distributed across the protein. A method of doing this is described in more detail at page 8, lines 15-23 and some possible results are shown in Figs. 1-6. Where a native sequence has a Tg of 170°C or less (page 3, line 30 of applicant's specification), the instant inventors found that one can identify sequences having a higher Tg and select these sequences for expression as individual gelatin-like polypeptides. The inventors also found that polypeptides having the selected sequences have a calculated Tg of higher than 180°C. Furthermore some are found also to have a measured Tg of higher than 180°C, for example as described in applicant's Example 2 and to have significantly improved properties when used as stabilizers of lyophilized compositions: the lyophilized composition have an improved thermal stability.

The property that the polypeptide has a calculated Tg of higher than 180°C can therefore be understood to be a property which is obtained by specifically selecting an appropriate sequence when making the polypeptide. This selected property is believed not to be an inherent property of the native sequence or of any other known polypeptide.

Turning now to consider the cited references in more detail, as stated above, applicant's claims as now amended are believed novel over either of Chang et al. '801 or Chang et al. '646).

Chang et al. '801 and Chang et al. '646 describe in broad terms the production of recombinant gelatins in microbial hosts. These gelatins are intended to replace natural gelatins and avoid risks such as bovine spongiform encephalitis ("BSE"). As described in the references, they are produced by expressing natural sequences, or fragments or variants thereof, in other host organisms. As acknowledged in the Office action, there is

no disclosure in either reference of polypeptides having a higher Tg than 180 degrees Celsius or of selecting sequences which might correspond with polypeptides having a higher Tg than 180 degrees Celsius.

The Chang et al. references provide a general disclosure of a large variety of polypeptide sequences, of various sizes, molecular weight and so on which disclosure does not anticipate a lyophilized composition for which polypeptides having sequences providing a Tg higher than 180 Celsius are specifically selected as stabilizers. Natural gelatin-like proteins, which Chang et al. '801 and Chang et al. '646 intend to replace, are believed to have a Tg of below 170° C. There is, therefore, no disclosure in Chang et al. '801 or in Chang et al. '646 of the lyophilized compositions claimed in applicant's amended claim 1 or of the process of preparing such lyophilized compositions that si claimed in amended claim 9.

The only features which are purposefully varied in Chang et al. '801 and Chang et al. '646 are molecular weight (size; Chang et al. '801 page 32, lines 27-36; Chang et al. '646 page 31, lines 27-36), degree of proline hydroxylation (helix formation; Chang et al. '801 page 35, lines 21-32; Chang et al. '646 page 34, lines 21-32) and degree of cross-linking (Chang et al. '801 page 37, lines 25-38; Chang et al. '646 page 36, lines 25-38). It is believed by applicant that none of these variations would lead to a gelatin-like polypeptide as recited in applicant's claims.

Nor is there any disclosure in either Chang et al. reference of being able to identify or make polypeptides with a higher Tg, or that such a higher Tg would have any specific effect or be useful as a stabilizer of lyophilized compositions.

Chang et al. '646 mentions the use of recombinant gelatins as “stabilizers” only on page 29, line 10, and on page 61, paragraph 3. This disclosure is general, and does not remotely suggest modifying the Tg of a recombinant gelatin-like polypeptide, how the

Tg might be modified or what the effect would be. In summary, it is believed that none of the recombinant polypeptides of Chang et al. '646 have a Tg above 180°C. Accordingly applicant's amended claims are, furthermore believed not anticipated by Chang et al. '646 for these additional meaningful reasons.

Chang et al. '801 (filed on the same day as Chang et al. '646) appears to disclose vaccines comprising gelatin as a stabilizer. However, the gelatins are described broadly in much the same way as in Chang et al. '646. Essentially, according to Chang et al. '801, any recombinantly produced gelatin can be used as a vaccine stabilizer, replacing natural gelatin. Chang et al. '801's disclosure thus appears to relate to the purity and uniformity of the expressed material, and not to any particular measures for improving thermal stability of lyophilized compositions. As stated on page 31, last line of Chang et al. '801:

“...the present invention provides recombinant gelatins comprising uniform molecules of a specified molecular weight...”.

As in Chang et al. '646, the only variables of the gelatin polypeptides described in Chang et al. '801 are: molecular weight (size; page 32, line 12-36), degree of proline hydroxylation (helix formation; page 34, lines 31 – page 35 line 32) and degree of cross-linking (p37, line 25-38).

Chang et al. '801 mentions that stability of vaccines is a problem and that it is an object to provide improved stabilizing agents which include recombinant gelatins (page 59, line 25-26). Page 62, line 19 onwards of Chang et al. '801 describes what kind of gelatins can be used as vaccine components, providing a generalized description of a large variety of recombinantly produced gelatins of different molecular weights, and so on. See for example page 64, lines 36-38 which read as follows:

"The present invention provides for the production of recombinant gelatins specifically tailored, through manipulation of cross-linking, hydroxylation, molecular weight or any combination thereof, to possess thermal characteristics suited for particular applications."

Again, there is no disclosure of selecting or making polypeptides with an increased T_g or of using such polypeptides as stabilizers of lyophilized compositions. It is also believed that none of the recombinant polypeptides of Chang et al. '801, any more than did those of Chang et al. '646, has a T_g above 180°C. It follows that applicant's amended claims are, therefore, novel and not anticipated by Chang et al. '801.

To verify the above conclusions, applicant has calculated the T_g of some of the sequences disclosed in Chang et al. '801 and Chang et al. '646, noting that the sequences in both documents are the same. The table below shows the results of these calculations using the method of Y. Matveev in. Food Hydrocolloids Vol. 11 no. 2, pp. 125-133, 1997. In each case the T_g is significantly below 180 degrees Celsius:

SEQ ID No.:	Calculated T_g (deg C) according to the method of Matveev
15	124.2
25	164.3
30	137.5
31	156.3
33	174.1

Unobviousness of the Claimed Invention

Furthermore, although no allegations as to unpatentability of applicant's claimed invention have been made, nor does applicant believe they should be, nevertheless it is believed helpful to advance the prosecution of this application to explain why applicant believes the subject matter of amended claims 1 and 9 was not obvious to a person of ordinary skill in the art prior to applicant's invention.

It is noted that unlike Chang et al. '646, Chang et al. '801 relates to the use of recombinant gelatin in vaccine compositions. One difference which applicant's amended

claims 1 and 9 have from Chang et al. '801 is that claims 1 and 9 call for the use of a recombinant gelatin-like polypeptide as a stabilizer of lyophilized compositions which gelatin-like polypeptide has a calculated glass transition temperature (T_g) of higher than 180 degrees Celsius. In contrast, Chang et al. '801 discloses that any recombinantly produced collagen/gelatin can be employed as stabilizers in vaccine compositions, i.e. polypeptides of a wide variety of molecular weights, a wide degree of hydroxylation and/or cross-linking can be employed.

One effect of this difference is that applicant's claimed lyophilized pharmaceutical compositions have an improved stability. An objective technical problem addressed by applicant's invention, in view of Chang et al. '801, is to provide an improved stabilizer of lyophilized compositions. This problem is solved by identifying and making recombinant or synthetic gelatin-like polypeptides having a calculated T_g of above 180 degrees Celsius, which in some cases have been shown to also have a higher measured T_g.

However, starting from Chang et al. '801, the skilled person trying to solve the above objective problem would have no indication as to what characteristic of the polypeptides needs to be purposefully modified or how to this can be done. The skilled person would not be led to screen polypeptides for regions having an increased calculated T_g, as she or he would not even know that variation in calculated T_g exists across polypeptides. Furthermore the person of ordinary skill in the art would not know that increasing the calculated T_g would also result in an increase of the measured T_g, and an increase in thermal stability. Furthermore, neither Chang et al. '646 nor any of the other documents on file, were they to be combined with Chang et al. '801, which applicant sees no reason to do, would lead to the claimed subject matter. The skilled person would, therefore, not arrive at the subject matter of the invention claimed in claims 1 and 9.

Accordingly, claims 1 and 9 are believed patentably distinguished from Chang et al. '801, Chang et al. '646 or any other art of record or known to applicant, and therefore allowable.

Dependent Claims

Claims 2-7 and 10-23 depend either directly or indirectly from either claim 1 or claim 9, and are therefore believed allowable with claims 1 and 9 for the reasons that claims 1 and 9 are believed allowable. Dependent claims 2-7 and 10-23 are furthermore believed clearly and patentably distinguished from the art of record, and therefore allowable, by the additional meaningful limitations they recite.

For example, each of claims 4, 10 and 11 specifically recites that the glass transition temperature of the recombinant or synthetic gelatin-like polypeptide is higher than 190 degrees Celsius, which is not remotely suggested by the references of record, and claims 21-23 recite that the recombinant or synthetic gelatin-like polypeptide is higher than 200 degrees Celsius, which is not remotely suggested by the references of record.

Double Patenting

Claims 1-7 and 9-20 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10/567,078. Applicant respectfully requests that this rejection be reconsidered and withdrawn because no claim of Application No. 10/567,078 discloses or suggests a lyophilized composition or method of preparing same which employs a recombinant or synthetic gelatin-like polypeptide having a calculated glass transition temperature of higher than 180 degrees Celsius, as is required by each of amended claims 1-7 and 9-20 and new claims 21-23 of the instant application.

Conclusion

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Favorable reconsideration and allowance are earnestly solicited. If for any reason the Examiner feels that consultation with Applicant's representative would be helpful in the advancement of the prosecution, the Examiner is invited to call the undersigned practitioner below for an interview.

Respectfully submitted,

By: /Roger Pitt/
Roger Pitt
Reg. No. 46,996 Ph: (212) 536-4867

KIRKPATRICK & LOCKHART PRESTON GATES ELLIS LLP
599 Lexington Avenue (33rd Floor)
New York, NY 10022-6030

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